REMARKS

Upon entry of the present amendment, claims 1-14, 16, 20, 25-36, 38-50, and 52 will be pending. Applicants have amended claims 1, 3, 4, 8, 11, 16, 20, 25, 26, 32, 34, 36, and 52, and cancelled claims 15, 17-19, 21-24, 37, and 51. Support for these amendments can be found throughout the application as filed, e.g., at page 5, lines 7-27; page 7, lines 1-17; page 8, lines 15-19; page 11, lines 24-26; page 13, lines 17-19; page 13, line 28, to page 14, line 5; the Examples at pages 24-28; and the claims as filed, *inter alia*. No new matter has been added.

In addition, the specification has been amended to refer to the trademark CYDYES™, and to insert the generic description "cyanine-derived fluorescent dyes." This description was part of the general knowledge in the art at the time of filing and thus does not represent new matter.

Restriction/Species Selection

At page 2 of the Office Action mailed on April 9, 2007 (the "Office Action"), the provisional election of the species a(iii) immobilization via MHC molecule via biotin-streptavidin interaction from List II and species a(ii) anti-CD11a from List III is noted. Applicants hereby confirm this selection of species, and request that the remaining species be considered upon a finding that the generic claim is allowable.

Applicants further note that claims 24 and 25 were listed at page 3 as both under consideration and withdrawn. Applicants submit that claim 25 properly belongs to the group of claims under consideration. As claim 24 has been cancelled the point is moot with regard thereto.

Information Disclosure Statement

Applicants thank the Examiner for making the required corrections to the Form PTO-1449 as noted at page 3 of the Office Action.

Oath/Declaration

Applicants submit herewith a replacement declaration including a corrected signature page for inventor Gregory Carven, and request that the objection thereto be withdrawn.

Objection to the Specification

At page 4 of the Office Action, the use of the alleged trademark "CY" was noted. Applicants can find no evidence that CY by itself, or terms like "Cy3" and "Cy5" are trademarks; they are merely simplified names proposed by Ernst et al., "Cyanine dye labeling reagents for sulfhydryl groups," Cytometry. 1989;10(1):3-10, and adopted by the scientific community as a known and useful shorthand. Therefore, applicants submit that no amendment to the specification with regards to the use of "CY" is needed. The term CYDYE™, however, which appears at page 23, is a trademark, and the specification has been appropriately amended to include the generic terminology. Applicants therefore request withdrawal of the objection to the specification.

Claim Objections

Claims 21-24 were objected to at page 4 of the Office Action for improperly referring to claim 18. The Examiner correctly surmised that they were intended to depend from claim 19. Applicants have cancelled those claims, however, and so submit that the objection thereto is moot and request withdrawal thereof.

Claim Rejections under 35 U.S.C. §112

At pages 4-5 of the Office Action, claim 8 was rejected as allegedly indefinite for the use of the term "another molecule." While applicants do not concede that this term is indefinite (one of skill in the art would recognize that it encompasses molecules other than those listed, for use in immobilizing the MHC molecules on the substrate; a number of such molecules are known in the art), applicants have amended claim 8 to delete the phrase, and thus request withdrawal of the rejection under 35 U.S.C. § 112.

Claim Rejections under 35 U.S.C. §102

At pages 5-6 of the Office Action, claims 1, 11, 12, and 16 were rejected as allegedly anticipated by Webb et al. (WO 97/46256).

Claim 1 as amended recites:

> 1. An array comprising (i) a substrate, (ii) anti-factor antibodies specific for secreted factors immobilized on the substrate, and (iii) a plurality of MHC molecules complexed with antigen-derived peptides immobilized in spatially-distinct areas on the substrate, wherein one or more groups of said spatially-distinct areas are configured to allow incubation of all the areas within the group with one sample, and wherein each group comprises a plurality of different MHC-peptide complexes.

Webb et al. discloses synthetic antigen-presenting matrices, e.g., insect cells that express MHC molecules on their surface, or synthetic matrices having a support with at least the extracellular portion of an MHC linked thereto (see the abstract and page 6, lines 3-30), that are used to activate CD4+ T cells or to shift an activated population towards either a Th1 or Th2 response, as desired (see the abstract). Webb et al. further disclose that "accessory molecules" can also be linked to the support (see page 6, lines 7-8). However, Webb et al. neither teaches nor suggests arrays including anti-factor antibodies specific for secreted factors immobilized on the substrate, or arrays in which one or more groups of said spatially-distinct areas are configured to allow incubation of all the areas within the group with one sample, wherein each group comprises a plurality of different MHC-peptide complexes, as recited in amended claim 1. For at least these reasons, Webb et al. fails to anticipate the claimed arrays.

At pages 6-7 of the Office Action, claims 1-3, 6, 7, 11, 15, and 16 were rejected as allegedly anticipated by Brown et al., US 2003/0044389.[1] Brown et al. relates generally to cell profiling microarrays, and notes that "binding probes of interest may include ... antigen-bearing MHC constructs" (see page 2, para 26). Further discussion of analysis of T cells is included at page 7, para. 74, which describes the use of a "passive profile" with arrays of T cells, in which the sample is circulated or flowed over all or some of the array. However, Brown et al. neither teaches nor suggest arrays including anti-factor antibodies specific for secreted factors

[1] Applicants do not by these remarks concede that Brown et al. is a proper prior art reference against the pending claims, and reserve the right to swear behind the Brown et al. reference in the future.

immobilized on the substrate as recited in amended claim 1. Furthermore, with respect to claim 2, applicants disagree with the Office's contention at page 6 that "Brown et al. teaches the MHC-molecules in all of the spatially-distinct areas are the same (p2, paragraph [0025])." Applicants can find no teaching, in the cited section or elsewhere in Brown et al., relating to an array of MHC-peptide complexes wherein all of the MHC-molecules are the same. Nor, contrary to the Office's assertion at page 7, is there any teaching that the MHC molecules comprise Class I, Class II, or both Class I and II MHC molecules (as recited in claim 16). For at least these reasons, Brown et al. fails to anticipate the claimed arrays.

In light of the amendments and arguments set forth herein, applicants submit that the claimed arrays are novel over the cited art, and request withdrawal of the rejection under 35 U.S.C. § 102.

Claim Rejections under 35 U.S.C. §103

A number of rejections of the pending claims under 35 U.S.C. §103 were set forth at pages 7-20 of the Office Action. As a first matter, applicants note that to establish a prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). Furthermore, if an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). See MPEP 2143.03.

Applicants will now respond to each rejection in turn.

Webb et al. in view of Taylor et al. or Tom-Moy et al.

At pages 8-10 of the Office Action, claims 2-7 and 15, which ultimately depend from claim 1, were rejected as allegedly obvious over Webb et al. in view of Taylor et al. (USPN 6103479). At pages 10-11 of the Office Action, claims 8, 9, and 17, which ultimately depend from claim 1, were rejected as allegedly obvious over Webb et al. in view of Tom-Moy et al. (USPN 6235488). Applicants respectfully traverse.

The relevant disclosure of Webb et al. is set forth above.

Taylor et al. relates generally to non-uniform micro-patterned arrays that allow multiple types of cell interactions to be studied simultaneously (see the abstract); the arrays of Taylor et al. are arrays of cells. Taylor et al. was cited by the Office as describing the use of arrays comprising about 10, 50, or 100 different spatially-distinct areas on the substrate, each having different specific cell binding molecules, and for the use of substrates comprising glass or silicon.

Tom-Moy et al. was cited by the Office as teaching the substitution of streptavidin for avidin. Applicants do not dispute that the two molecules are functional equivalents.

Both Taylor et al. and Tom-Moy et al. fail to teach or suggest the claim elements missing from Webb et al., as set forth above. For example, the combination of Webb et al. and Taylor et al. or Tom-Moy et al. fails to teach or suggest arrays including anti-factor antibodies specific for secreted factors immobilized on the substrate, or arrays in which one or more groups of said spatially-distinct areas are configured to allow incubation of all the areas within the group with one sample, wherein each group comprises a plurality of different MHC-peptide complexes, as recited in amended claim 1.

Therefore, as the combination of Webb et al. and Tom-Moy et al., or of Webb et al. and Taylor et al., does not teach or suggest every limitation of the claims, the Office has failed to make a *prima facie* case of obviousness.

Webb et al. in view of Abraham et al. and Mikesell et al.

At pages 11-13 of the Office Action, claim 13, which ultimately depends from claim 1, was rejected as allegedly obvious over Webb et al. in view of Abraham et al. (J. Immunol. 167:5193-5201 (2001)) and Mikesell et al. (USPG PUB No. 2002/0095024). Applicants respectfully traverse.

The relevant disclosure of Webb et al. is set forth above. Abraham et al. and Mikesell et al. were cited by the Office as teaching the use of anti-CD11a antibodies as costimulatory antibodies. Applicants do not dispute that anti-CD11a antibodies were known to be costimulatory molecules. However, Abraham et al. and Mikesell et al. fail to teach or suggest

arrays including anti-factor antibodies specific for secreted factors immobilized on the substrate, or arrays in which one or more groups of said spatially-distinct areas are configured to allow incubation of all the areas within the group with one sample, wherein each group comprises a plurality of different MHC-peptide complexes, as recited in amended claim 1.

Therefore, the combination of Webb et al., Abraham et al., and Mikesell et al. does not teach or suggest every limitation of the claims; thus, the Office has failed to make a prima facie case of obviousness.

Webb et al. in view of Butler et al.

At pages 13-14 of the Office Action, claims 19, 20, 22, and 25 were rejected as allegedly obvious over Webb et al. in view of Butler et al. (J. Immunol. 169:3700-3709 (2002)). Applicants note that while claims 19 and 22 have been cancelled, the subject matter of those claims is subsumed in the scope of the pending claims, e.g., claim 1 and claim 16, which ultimately depends from claim 1. Applicants respectfully traverse the rejection, insofar as it may apply to the pending claims.

The relevant disclosure of Webb et al. is set forth above. Butler et al. describe methods that include ELISAs for IL-4, IL-13, and IFN-gamma, and ELISPOT IL-4 assays. A typical ELISPOT assay is conducted in a multiwell plate, usually a 96 well plate. Butler et al. used commercially-available ELISA and ELISPOT kits that use multiwell plates (see page 3701, left column, section entitled *ELISA and ELISPOT*). As one of skill in the art will appreciate, these kits are configured such that each well represents a single assay condition, thus all of the cells in a sample, i.e., all the cells in a well that are in liquid communication with each other, are provided with the same conditions. Dependent claims 20 and 25 incorporate by reference all of the limitations of claim 1, from which they depend. As noted above, amended claim 1 recites "one or more groups of said spatially-distinct areas are configured to allow incubation of all the areas within the group with one sample, wherein each group comprises a plurality of different MHC-peptide complexes." Nothing in Webb et al. or Butler et al., alone or together, teaches or suggests the use of an array so configured; each well includes only a single assay condition, and

unlike in the present arrays there is no fluid communication between the wells to allow the incubation of multiple wells with one sample, as required by claim 1.

Furthermore, one of skill in the art at the time of the invention would not have expected that a configuration as recited in claim 1 would work. This is primarily because the factors secreted by the activated T cells are, by their very nature, soluble; they are for the most part small proteins and would be expected to diffuse readily through the medium. Such solubility is generally required in order for these factors to perform their functions in cell signaling and intercellular communication. Thus, one of skill in the art would have expected that stimulating a single sample of T cells with a heterogeneous mixture of different MHC-peptide complexes in a single group would result in the signals being lost, compromised, or degraded due to diffusion of the secreted factors into the incubation media, such that it would be unlikely that faint signals (e.g., from low number responders) or distinct signals (e.g., from a single area of MHC-peptide complexes) would be detectable. Examples 2 and 3 of the present application demonstrate that this is not the case, but prior to the present invention one of skill in the art would not have had a reasonable expectation that such a configuration would produce useful results.

The results seen in Butler et al. do not provide any expectation of success. As is commonly known in the art, the diameter of the wells in the 96 well plates that are used in typical ELISPOT assays is about 7 mm. In contrast, the size of a typical array element is about two orders of magnitude smaller: the present application at page 14, lines 12-16, suggests a size of about 50 microns, and Figure 2A shows multiple spots within a 240 micron wide area. Thus, one of skill in the art would have expected diffusion to be an issue in the claimed arrays. Diffusion is clearly not an issue in multiwell plates, each well of which represents homogeneous assay conditions, the success of a method using multiwell plates would not predict success in methods using arrays.

The ability to assay a number of MHC-peptide complexes in a single sample is an important advantage of the present arrays, since often the number of T cells available from a patient is limited, as noted in Lehmann et al., USPN 5939281, Col. 21, lines 51-55,

> The number of cells available from patients can be limiting; one million cells can be obtained from one milliliter of blood and usually fifty milliliters of

blood is available per patient (i.e. fifty million cells may be the total cells available for the assay).

This limited number of cells, coupled with the expected low frequency of the T cells of interest (see the present application, e.g., at page 11, lines 3-20, which notes that the frequency of T cells of interest is likely to be on the order of 10^{-3} to 10^{-6}), means that the ability of the present arrays to incubate a number of MHC-peptide complexes in a single sample of a size compatible with clinical use increases the likelihood that such low frequency T cells will be detected. In methods such as standard ELISPOT or cytokine capture assays, where the sample would necessarily need to be split over a number of different wells to expose the sample to a reasonable number of MHC-peptide complexes, the chances of the T cells of interest happening to be present in the well with the correct MHC-peptide complex would be very low indeed.

For at least these reasons, applicants submit that the pending claims are not obvious over Webb et al. in view of Butler et al.

Webb et al. in view of Lehmann et al.

At pages 14-16 of the Office Action, claims 19, 20, 22, and 25 were rejected as allegedly obvious over Webb et al. in view of Lehmann et al. (USPN 5939281). Applicants note that while claims 19, 22, and 25 have been cancelled, the subject matter of those claims is subsumed in the scope of claims 1, 16, and 17. Applicants respectfully traverse the rejection, insofar as it may apply to the pending claims.

The relevant disclosure of Webb et al. is set forth above. Lehmann et al. disclose cytokine capture assays. Like the ELISPOT assays described in Butler et al., the assays disclosed in Lehmann et al. are performed in multiwell plates. Lehmann et al. note that plates with 50 microliter wells can be used, but again, each well contains only a single peptide. As noted above, amended claim 1 recites "one or more groups of said spatially-distinct areas are configured to allow incubation of all the areas within the group with one sample, wherein each group comprises a plurality of different MHC-peptide complexes." Nothing in Webb et al. or Lehmann et al., alone or together, teaches or suggests the use of an array so configured; each well includes only a single assay condition, and there is no fluid communication between the

wells to allow the incubation of multiple wells with one sample, as required by claim 1. Furthermore, there would be no reasonable expectation of success, for at least the reasons set for above with regards to Butler et al.

Since every dependent claim incorporates by reference all of the limitations of the claim(s) from which it depends, and the combination of Webb et al. and Lehmann et al. does not teach or suggest every limitation of the claim, the Office has failed to make a prima facie case of obviousness.

Webb et al. in view of Butler et al. or Lehmann et al. and Taylor et al. or Tom-Moy et al

Claim 21 was rejected at pages 16-18 of the Office Action as allegedly obvious over Webb et al. in view of Butler et al. or Lehmann et al. and further in view of Taylor et al. Applicants note that while claim 21 has been cancelled, the subject matter of that claim is subsumed in the scope of the pending claims, e.g., claim 5, which depends from claim 1. In addition, claim 23 was rejected at pages 18-20 of the Office Action as allegedly obvious over Webb et al. in view of Butler et al. or Lehmann et al. and further in view of Tom-Moy et al. Applicants note that while claim 23 has been cancelled, the subject matter of that claim is subsumed in the scope of the pending claims, e.g., claim 9, which depends from claim 1.

Applicants respectfully traverse the rejection, insofar as it may apply to the pending claims.

The disclosures of Webb et al., Butler et al., Lehmann et al., Taylor et al., and Tom-Moy et al. are as set forth above. Nothing in the cited references, alone or together, teaches or suggests the use of an array "configured to allow incubation of all the areas within the group with one sample" as recited in amended claim 1. To the contrary each well includes only a single assay condition, and there is no fluid communication between the wells to allow the incubation of multiple wells with one sample, as required by independent claim 1. Since every dependent claim incorporates by reference all of the limitations of the claim(s) from which it depends, Applicants submit that pending claims 5 and 9 are not obvious over the cited art.

In light of the amendments and arguments set forth herein, Applicants submit that the claimed arrays are not obvious over the cited art, and request withdrawal of the rejection under 35 U.S.C. § 103.

Additional Art Not Relied on by the Office

Applicants note that pages 20-21 of the Office Action include a list of additional references made of record but not relied upon by the Office. Applicants submit that the pending claims are novel and not obvious over this additional art for at least the reasons set forth herein.

Conclusion

For at least the reasons set for herein, and in light of the amendments made herein, Applicants submit that the pending claims are allowable, and request early notification thereof. If the Examiner feels that it would further prosecution of the present application, she is invited to telephone the undersigned at (617) 956-5985.

The Petition for Extension of Time fee is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 07917-212001.

Respectfully submitted,

Date: Oct. 9, 2007

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